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Débarre, Florence ; Yeaman, Sam ; Guillaume, Frédéric

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DOI: <https://doi.org/10.1086/681717>

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ZORA URL: <https://doi.org/10.5167/uzh-116015>

Journal Article

Published Version

Originally published at:

Débarre, Florence; Yeaman, Sam; Guillaume, Frédéric (2015). Evolution of quantitative traits under a migration-selection balance: when does skew matter? *The American Naturalist*, 186:S37-S47.

DOI: <https://doi.org/10.1086/681717>



CHICAGO JOURNALS



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Source: *The American Naturalist*, (-Not available-), p. S000

Published by: [The University of Chicago Press](#) for [The American Society of Naturalists](#)

Stable URL: <http://www.jstor.org/stable/10.1086/681717>

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# Evolution of Quantitative Traits under a Migration-Selection Balance: When Does Skew Matter?\*

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Online enhancement: appendix.

**ABSTRACT:** Quantitative-genetic models of differentiation under migration-selection balance often rely on the assumption of normally distributed genotypic and phenotypic values. When a population is subdivided into demes with selection toward different local optima, migration between demes may result in asymmetric, or skewed, local distributions. Using a simplified two-habitat model, we derive formulas without a priori assuming a Gaussian distribution of genotypic values, and we find expressions that naturally incorporate higher moments, such as skew. These formulas yield predictions of the expected divergence under migration-selection balance that are more accurate than models assuming Gaussian distributions, which illustrates the importance of incorporating these higher moments to assess the response to selection in heterogeneous environments. We further show with simulations that traits with loci of large effect display the largest skew in their distribution at migration-selection balance.

**Keywords:** local adaptation, gene flow, migration selection balance, quantitative genetics, skew, major gene.

## Introduction

Understanding how adaptations are shaped by the balance between divergent selection and migration is an important problem in evolutionary biology. Quantitative-genetic models can be used to address this question when the traits controlling adaptation are continuous. Even in the case of sub-

divided populations under divergent selection (so-called migration-selection models), it is common to use the simplifying assumption that the local distributions of genotypic and phenotypic values are Gaussian (Hendry et al. 2001; Ronce and Kirkpatrick 2001; Lopez et al. 2008; Tufto 2010), and formulas derived in this context have been used in empirical studies (Saint-Laurent et al. 2003; Moore et al. 2007). Under divergent selection, however, the trait difference between local and immigrant individuals is susceptible to generating asymmetries (skew) in the local distributions of traits, thus violating the Gaussian model assumption. As shown by Yeaman and Guillaume (2009), such departures from normality can cause quantitative-genetic models to significantly underestimate the amount of phenotypic divergence between populations. Indeed, the discrepancy between Yeaman and Guillaume's individual-based simulations and predictions under the Gaussian approximation (based on Hendry et al. 2001) was strongly correlated with the amount of genetic skew in the trait under divergent selection.

The fact that higher moments of the distribution of genotypic or phenotypic values, such as skew, influence the response to selection of a quantitative trait has long been recognized (Barton and Turelli 1987; Turelli and Barton 1990, 1994; Bürger 1991; Rice 2002). Nevertheless, it is usually acknowledged that when the quantitative traits are determined by many loci of small effect, the Gaussian approximation is sufficiently robust to model the evolutionary dynamics of the traits (Turelli and Barton 1994). This still holds for migration-selection models when the trait under divergent selection is polygenic, with small effects at many loci (Tufto 2000; Huisman and Tufto 2012). From the results of Yeaman and Guillaume (2009), this was likely because genetic skew is relatively limited in this context, but other explanations have not been conclusively ruled out.

\* This issue originated as the 2014 Vice Presidential Symposium presented at the annual meetings of the American Society of Naturalists.

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Am. Nat. 2015. Vol. 186, pp. S000–S000. © 2015 by The University of Chicago. 0003-0147/2015/186S1-5588\$15.00. All rights reserved.  
DOI: 10.1086/681717

For instance, Huisman and Tufto (2012) suggested that the time at which the genetic variance is evaluated (before vs. after migration or selection) could also play a role.

Different genetic architectures (i.e., the number and effect size of loci contributing to divergence) may, however, produce different results. In particular, the Gaussian approximation will be violated when a trait is controlled by a mix of major and minor genes. Such architectures may be common (Lande 1983; Orr 2001; Slate 2005), and fixation of large alleles at major loci is expected when a population is subject to a sudden shift in its environment and has to evolve a new optimum phenotype (Lande 1983; Gomulkiewicz et al. 2010). Similarly, Yeaman and Whitlock (2011) showed that, under migration-selection balance, the evolution of the genetic architecture of traits under divergent selection results in adaptation being controlled by fewer or more tightly linked loci. This is possible when the effects of each locus can themselves evolve by accruing mutational effects over generations. Major loci are then favored because they are under stronger selection and avoid being swamped by gene flow (Yeaman and Whitlock 2011; Geroldinger and Bürger 2014). Yeaman and Guillaume (2009) further showed that such architectures were causing the strongest genetic skew and, hence, the strongest underestimation of population divergence by the Gaussian approximation model (Hendry et al. 2001). Although Yeaman and Guillaume (2009) provided an attempt at accounting analytically for genetic skew, there is currently no model able to accurately predict population phenotypic divergence in the presence of a non-Gaussian distribution of trait values.

In this study, we provide an expression of the expected population phenotypic divergence at migration-selection equilibrium that does not rely on the assumption of Gaussian distributions of genotypic values. Our expression improves previous derivations (e.g., Hendry et al. 2001; Lopez et al. 2008) by incorporating the skew (third moment) of that distribution. We then use individual-based simulations to explicitly link the amount of genetic skew in the trait under divergent selection with the details of its genetic architecture. We show, first, that by taking account of the skew, we improve the accuracy of the analytical model and, second, that genetic architectures including a major locus of large effect lead to the largest population divergence at equilibrium and cause the largest skew in the trait distribution. Finally, we confirm that disagreement of simulation results with the Gaussian approximation is not caused by misestimation of the genetic variance at equilibrium.

### Model

To make our point about the importance of skew, we consider the simple but classical setting of a population inhabiting an environment with two different habitat types pres-

ent in equal frequencies (as in Hendry et al. 2001; Ronce and Kirkpatrick 2001; Yeaman and Guillaume 2009; Débarre et al. 2013). We focus on the migration-selection life cycle described in Hendry et al. (2001; the argument remains the same for Hendry et al.'s selection-migration life cycle). The aim of this section is to provide an analytical expression of the equilibrium differentiation between the two habitats (i.e., the difference between the local mean traits at equilibrium) that includes higher moments of the distributions of traits such as skew.

We assume that both subpopulations are saturated and have the same high carrying capacities; we can therefore neglect the effect of genetic drift, and we can focus on frequencies (instead of densities). The two habitats have different environments: in each habitat, there is selection toward a local optimum  $\theta_i$ , and a quantitative trait determines how well individuals are adapted to their habitat; we denote by  $\Delta\theta = \theta_2 - \theta_1$  the difference between the two optima. Without loss of generality, we assume that  $\Delta\theta \geq 0$ . The quantitative trait under selection is coded by many unlinked, additive loci. In our analysis, we focus not on the exact combination of alleles determining the trait of an individual but only on the sum of the allelic effects; we use the term "genotypic value" to refer to this sum. The expressed phenotype,  $\zeta$ , on which selection acts, depends on the genotypic value  $z$  and on environmental effects  $z_E$ :  $\zeta = z + z_E$ . We denote the distribution of these environmental effects by  $\pi(z_E)$ , whose mean is 0 and whose variance is  $V_E$ , the same for all genotypes. The fitness of an individual expressing phenotype  $\zeta$  in habitat  $i$  is given by

$$w_i(\zeta) = \exp\left(-\frac{(\zeta - \theta_i)^2}{2\omega^2}\right). \quad (1a)$$

Further assuming weak selection (i.e., large  $\omega^2$ ), we can rewrite the fitness functions as quadratic functions:

$$w_i(\zeta) = 1 - \frac{(\zeta - \theta_i)^2}{2\omega^2}. \quad (1b)$$

The life cycle goes as follows: individuals reproduce in their local habitats (mating is at random), and they produce a large number of offspring (the distribution of offspring number is the same for all individuals). The adults then die; a proportion  $m$  of the juveniles disperse to the other habitat. Then selection occurs, because of differential survival of the juveniles, whose fitness is given by  $w_i$  (eq. [1b]). Finally, population regulation occurs to bring the subpopulations back to carrying capacity.

We denote by  $p_i^{(t)}(z)$  the frequency of genotype  $z$  in population  $i$  at time  $t$ , and by  $\bar{z}_i^{(t)} = \int_{-\infty}^{+\infty} zp_i^{(t)}(z)dz$  the local average genotypic value. This quantity is also equal to the mean phenotype in habitat  $i$  ( $\bar{\zeta}_i^{(t)} = \bar{z}_i^{(t)}$ ) because the mean of the

environmental effects is 0. We now show how each step of the life cycle affects the distribution of genotypic values.

### Reproduction

How reproduction affects the distribution of genotypic values in the population depends on the architecture of the trait and cannot be described in a general manner. In our model, mating occurs at random within a deme, and local populations are large enough for drift to be neglected. Moreover, the trait is determined additively (the genotypic value is given by the sum of the allelic effects). Hence, reproduction does not affect the local mean genotypic value. The way mutation affects the genotypic value of offsprings depends on the model (diallelic model, or model with evolvable effects) and is described in more detail below. Using the superscript “r” to refer to the postreproduction distributions, this means that  $\bar{z}_i^r = \bar{z}_i^{(r)}$ , while all the other moments of the distribution are affected by reproduction.

### Migration

In each habitat ( $i$ ), a fraction  $m$  of individuals disperse to the other habitat ( $j$ ). After dispersal, the distribution of genotypic values, denoted by  $p_i^m(z)$ , is therefore

$$p_i^m(z) = mp_j^r(z) + (1 - m)p_i^r(z). \quad (2)$$

### Selection

In a given habitat  $i$ , the fitness of an individual depends on its phenotype  $\zeta$ . Because of environmental effects, individuals with a genotype  $z$  will express a phenotype  $\zeta = z + z_E$  with probability  $\pi(z_E)$ . The average fitness in habitat  $i$  of individuals with genotype  $z$ ,  $W_i(z)$ , takes these environmental effects into account:

$$W_i(z) = \int_{-\infty}^{+\infty} \pi(z_E) w_i(z + z_E) dz_E, \quad (3)$$

and we define  $\bar{W}_i^m$ , the mean fitness in habitat  $i$  when selection occurs (i.e., after dispersal). After selection (differential survival), the frequency of genotype  $z$  in population  $i$  is given by

$$p_i^s(z) = \frac{W_i(z)}{\bar{W}_i^m} p_i^m(z). \quad (4)$$

### Regulation

The last step of the life cycle is density regulation, which brings the local densities back to carrying capacity. This step does not affect the distribution of genotypic values

(here again, drift is neglected), so that the final distribution is

$$p_i^{(t+1)}(z) = p_i^s(z). \quad (5)$$

We denote by  $\Delta \bar{z}_i^{(t)} = \bar{z}_i^{(t+1)} - \bar{z}_i^{(t)}$  the change in the mean trait in habitat  $i$  (hereafter we drop the time dependency, for notational simplicity). Given the life cycle detailed above, this is

$$\Delta \bar{z}_i = \left( \int_{-\infty}^{+\infty} z \frac{W_i(z)}{\bar{W}_i^m} p_i^m(z) dz \right) - \bar{z}_i. \quad (6)$$

To provide a more explicit expression for  $\Delta \bar{z}_i$ , we need to make the individual ( $W_i(z)$ ) and local mean fitness ( $\bar{W}_i^m$ ) explicit; this is where the assumption of weak selection (large  $\omega$ ) is useful. Using equation (1b), we obtain

$$\begin{aligned} W_i(z) &= 1 - \frac{(z - \theta_i)^2 + V_E}{2\omega^2}, \\ \bar{W}_i^m &= 1 - \frac{(\bar{z}_i^m - \theta_i)^2 + V_E + v_i^m}{2\omega^2}, \end{aligned} \quad (7a)$$

where  $v_i^m = \int_{-\infty}^{+\infty} (z - \bar{z}_i^m)^2 p_i^m(z) dz$  is the variance of the postdispersal distribution of genotypic values. We note that, using equation (2), we could express this quantity as a function of the postselection variance; doing so would, however, make our expressions considerably more complicated while not bringing much insight, since the link between pre- and post-reproduction distributions would still remain implicit.

Under weak selection (large  $\omega$ ), the relative fitness becomes

$$\frac{W_i(z)}{\bar{W}_i^m} \approx 1 - \frac{(z - \theta_i)^2 - (\bar{z}_i^m - \theta_i)^2 - v_i^m}{2\omega^2}, \quad (7b)$$

and we note that the environmental variance  $V_E$  has disappeared from this expression. We can now use equation (7b) in equation (6), and we obtain, after simplifications,

$$\Delta \bar{z}_i = \frac{2m(\bar{z}_j - \bar{z}_i)(\omega^2 - v_i^m) - \zeta_i^m + 2v_i^m(\theta_i - \bar{z}_i)}{2\omega^2}, \quad (8)$$

where  $\zeta_i^m = \int_{-\infty}^{+\infty} (z - \bar{z}_i^m)^3 p_i^m(z) dz$  is the third central moment of the postdispersal distribution of genotypic values. The quantity called skewness is a standardized version of this moment, defined as  $\zeta_i^m / (v_i^m)^{3/2}$ . In this article, we use the generic term “skew” to refer to the asymmetry of a distribution, while the symbol  $\varsigma$  specifically represents the third central moment of this distribution.

The equilibrium mean genotypic values ( $\bar{z}_1^*$ ,  $\bar{z}_2^*$ ) are found by solving the ( $\Delta \bar{z}_1 = 0$ ,  $\Delta \bar{z}_2 = 0$ ) system for  $\bar{z}_1$  and  $\bar{z}_2$ . The two habitats being symmetric (the two habitats are present in equal frequencies, host the same density of individuals, with equal migration rates), the equilibrium distributions will mirror each other, so that  $p_1^*(z - \theta_1) = p_2^*(\theta_2 - z)$  (the



asterisk refers to equilibria), and therefore we will have  $\theta_2 - \bar{z}_2^* = \bar{z}_1^* - \theta_1$ ,  $v_2^{m*} = v_1^{m*} = v^{m*}$ , and  $\zeta_2^{m*} = -\zeta_1^{m*} = -\zeta^{m*}$ . Note that  $\zeta_1^* \geq 0 \geq \zeta_2^*$ , because  $\theta_2 \geq \theta_1$ .

Defining  $D_{MS}^* = \bar{z}_2^* - \bar{z}_1^*$  as the equilibrium differentiation in this life cycle where dispersal (migration) precedes selection (MS), we finally obtain

$$D_{MS}^* = \frac{v^{m*} \Delta\theta + \zeta^{m*}}{v^{m*}(1 - 2m) + 2m\omega^2}. \quad (9)$$

This expression highlights that neglecting the asymmetry ( $\zeta^{m*}$ , which is positive, since  $\Delta\theta = \theta_2 - \theta_1 \geq 0$ ) leads to an underestimation of the actual differentiation. It also shows that the extent to which the asymmetry of the distribution contributes to the evolved differentiation depends on how much variance is maintained in the population.

By contrast, Hendry et al. (2001; HDT) found

$$D_{MS[HDT]}^* = \frac{v^* \Delta\theta}{v^*(1 - 2m) + 2m\omega^2} \quad (10)$$

when the phenotypic variance is small. Hendry et al. (2001) neglected the asymmetry of the distribution, used the variance after selection ( $v^*$ ) instead of the variance after migration ( $v^{m*}$ ; the two are the same in their model, since they assume that genetic variance is constant throughout the life cycle), and assumed Gaussian distributions of traits for the selection gradients.

The equilibrium differentiation hence depends on the model's parameters ( $m$ ,  $\omega$ ,  $\Delta\theta$ ) but also on the equilibrium values of other variables, the higher central moments of the equilibrium distribution of traits (variance and skew). Writing recursions for these higher moments would reveal that they themselves depend on even higher moments (fourth and fifth central moments), and so on. So we instead evaluate the variance and skew from simulation data, predict from these the equilibrium differentiations  $D_{MS}^*$  and  $D_{MS[HDT]}^*$ , and compare these to the actual differentiation in the simulations.

For a fairer comparison of our result with that of Hendry et al. (2001), we assume that the different moments can be measured only once in the life cycle, and we use the postselection variance ( $v^*$ ) and skew ( $\zeta^*$ ) in equation (9) when comparing the two expressions (see figs. 1, 3). We see, however, in figure 1, that the timing of measurement of these moments only weakly affects the results, so that the difference is indeed due to the skew of the distributions.

### Simulations

We now compare the accuracy of our formulas for the equilibrium differentiation with the outcome of individual-based simulations, for different values of the migration prob-

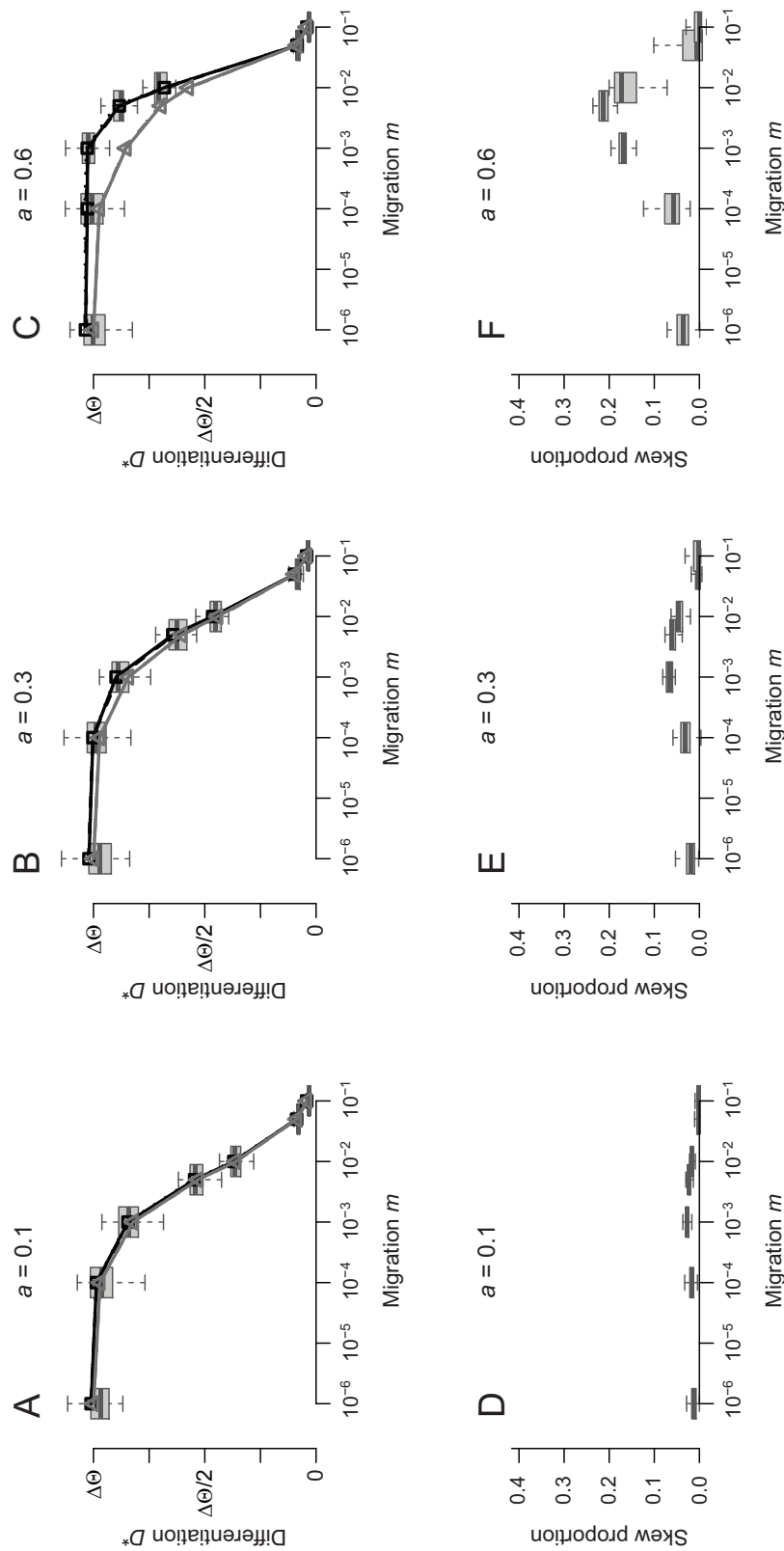
ability  $m$  and the strength of selection  $1/\omega^2$  and for two different genetic architectures: one with diallelic loci with fixed allele sizes, the other with loci carrying alleles with a continuum of possible values (model with evolvable effects). In both models, all alleles act additively to determine the genotypic value of an individual (there is no dominance or epistasis in the determination of the genotypic value, as is typically done in quantitative-genetic models).

The simulations were performed with a modified version of the software Nemo, version 2.2.0 (Guillaume and Rougemont 2006). Individuals are diploid, and each carries 20 unlinked quantitative loci determining the trait under stabilizing selection; random mating occurs in each patch after migration and selection among males and females, and each female is assigned a fecundity value drawn from a Poisson distribution with mean  $f = 3$ . The simulations were run for a number of generations large enough to ensure convergence of the variance and skew of the phenotypic distribution (4,000 generations in the diallelic model,  $10^6$  generations for the model with evolvable effects), and then the results were averaged over the last 200 generations in the diallelic model and the last  $2 \times 10^5$  generations for the model with evolvable effects. For simplicity, we set  $V_E = 0$  (i.e., we can identify genotypic and phenotypic values). The patch sizes are  $N = 1,000$  individuals, and the difference in phenotypic optima is  $\Delta\theta = 2$  (with optima  $\theta_2 = +1$  and  $\theta_1 = -1$ ). Migration is symmetrical between patches, with rates  $m$  ranging from  $10^{-6}$  to 0.1.

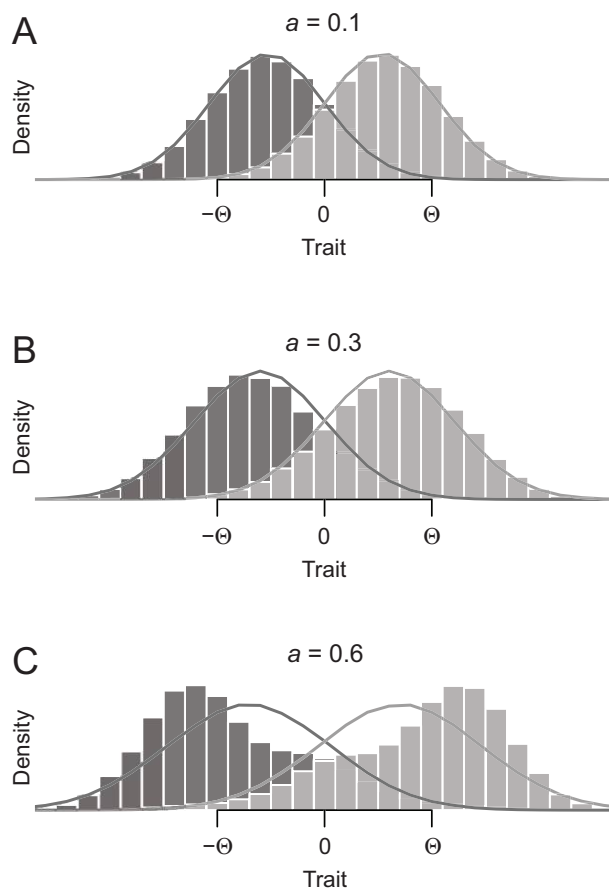
#### Diallelic Model with Fixed Effects at Each Locus

To assess how much the presence of a locus of major effect affected the evolved level of skew in the distributions of genotypic values, we ran a set of simulations with 20 loci of fixed effects. All loci are diallelic with effects of  $\pm 0.1$ , except one locus, the major locus, which contributes an effect of  $\pm a$ . Mutation at each locus occurs with rate  $\mu = 10^{-4}$  and simply swaps the sign of the allelic value. We note that, contrary to our assumption that reproduction does not change the local mean genotypic value, mutation does actually change the local mean genotypic value, pushing it toward 0 (when “+” and “−” alleles balance each other); we nevertheless assume that the mutation rate  $\mu$  that we used in the simulations remains small enough for this effect to be negligible.

Figure 1 presents comparisons between the two analytical predictions of the differentiation between patches ( $D_{MS}^*$  and  $D_{MS[HDT]}^*$ ) at equilibrium and the differentiations in the simulations, for values of  $a$  ranging from 0.1 (all loci have the same effect) to 0.6 (one locus dominates). When all loci have the same effect ( $a = 0.1$ ), very little skew is generated, even at intermediate dispersal (fig. 1D), and the Gaussian approximation (eq. [10]; gray in the figure) provides good



**Figure 1:** Output of the simulations when allelic effects are fixed, for different values of  $a$ , the effect of the major locus. A–C, Equilibrium phenotypic divergence between two patches in the diallelic simulations (box plots) and the corresponding expectations from equations (9) (rectangles and black lines) and (10) (triangles and gray lines) as a function of the migration rate, with three timings of evaluation of the variance and third moment (solid lines: with  $v^*$  and  $\zeta^*$ , the postselection variance and third moment, respectively; dashed lines: with  $v^m$  and  $\zeta^m$ , the postmigration variance and third moment, respectively). The dashed and dotted lines are hardly distinguishable from the solid lines. D–F, Proportion of the divergence due to the skew ( $\zeta^*/(\Delta\theta v^* + \zeta^*)$ ). In all panels,  $\omega^2 = 25$ .



**Figure 2:** Distributions of trait values in both patches at equilibrium, when  $m = 5 \times 10^{-3}$ , for different values of  $a$ , the effect of the major locus. The gray histograms are for the outcomes of the simulations (distribution in patch 2 is lighter). Superimposed are the corresponding Gaussian distributions, whose variances are the same as in the simulations and whose means are calculated from equation (10).

predictions for the equilibrium differentiation (see also fig. 2A). With a major-effect locus, however, the skew of the distribution of genotypic values is substantial (fig. 1F), especially at intermediate migration rates, and must be taken into account (see also fig. 2C). In other words, a diallelic model with equal effect sizes among loci approximates well the Gaussian expectation obtained under the infinitesimal model assumption, which breaks down when one locus explains most of the phenotypic divergence between populations.

Selection at the locus of effect  $a$  is stronger than that at other loci when  $a$  increases. As shown in figure 3A–3C, the frequencies of the “+” allele therefore reach more extreme values at the locus of effect  $a$ , while they remain around 0.5 at other loci (or when  $a = 0.1$ , which is the same effect size as at the other loci; this is because there are more loci than needed to reach the optimal trait values  $\pm \theta$ ). The

contribution of a locus of effect  $a$  to the third moment of the distribution is  $8a^3p_a(1-p_a)(1-2p_a)$ , where  $p_a$  is the frequency of the “+” allele at that locus. This contribution is lowest when  $p_a$  is equal to 1/2, 0, or 1 and is highest when  $p_a = 1/2 \pm 1/(2\sqrt{3})$  (i.e., approximately 0.21 or 0.79). Hence, the contributions to the third moment remain low when  $a = 0.1$ , but the major-effect locus generates skewness when  $a = 0.3$  and  $a = 0.6$ , driving the high value of the third moment for the trait that is reached for intermediate values of migration (see fig. 3E, 3F).

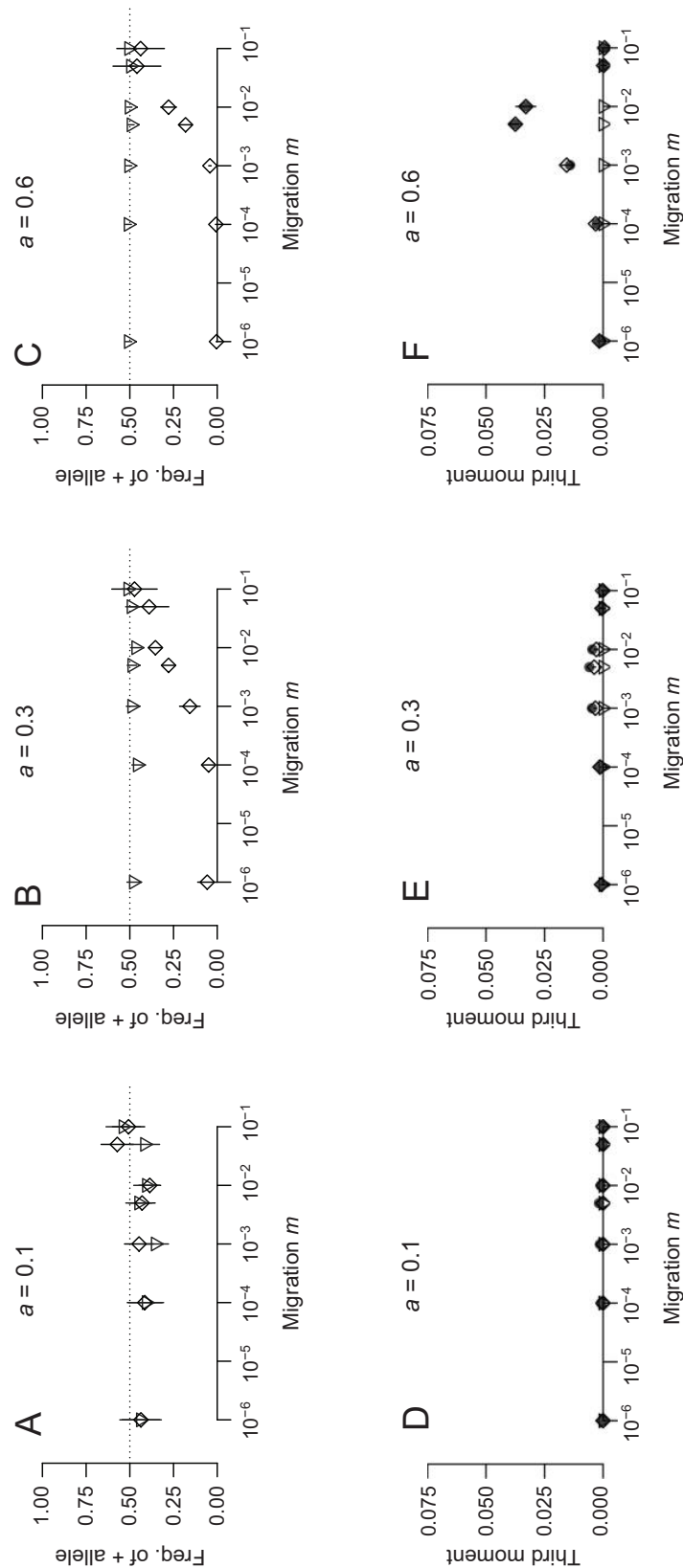
While  $D_{\text{MS[HDT]}}^*$  is a natural measure of differentiation under the Gaussian approximation (which often also includes the assumption of a constant variance), comparing only means might not be enough when the variance of the distributions is not fixed or when the distributions are skewed. We checked the robustness of our observations by evaluating two alternative measures of differentiation: the fraction of the distributions of traits in the two habitats that do not overlap and  $Q_{\text{ST}}$  (Spitze 1993; see fig. A1, available online), and we confirm that the conclusions using the difference between means in each habitat  $D^*$  still hold.

These simulations also indicate that the step of the life cycle at which the variance and skew are measured does not have a great influence on the results. We measured the variance and third central moment of the distributions of genotypic values at different steps of the life cycle, and we used these different evaluations in the formulas predicting the evolved differentiations (eqq. [9], [10]; black and gray, respectively, in the figure); these results are presented in figure 1A–1C, using the variance and skew after selection (solid lines) but also those after mating (superscript “r,” dashed lines) and after dispersal (superscript “m,” dotted lines). The analytical predictions using these different values of variance and skew are almost undistinguishable, which confirms that the main difference between the quality of the prediction of equations (9) and (10) is not the step at which the higher moments are estimated but indeed the skewness of the distributions of genotypic values. Taking this skew into account improves the match between the simulations and the analytical results, in particular with architectures that tend to generate skew.

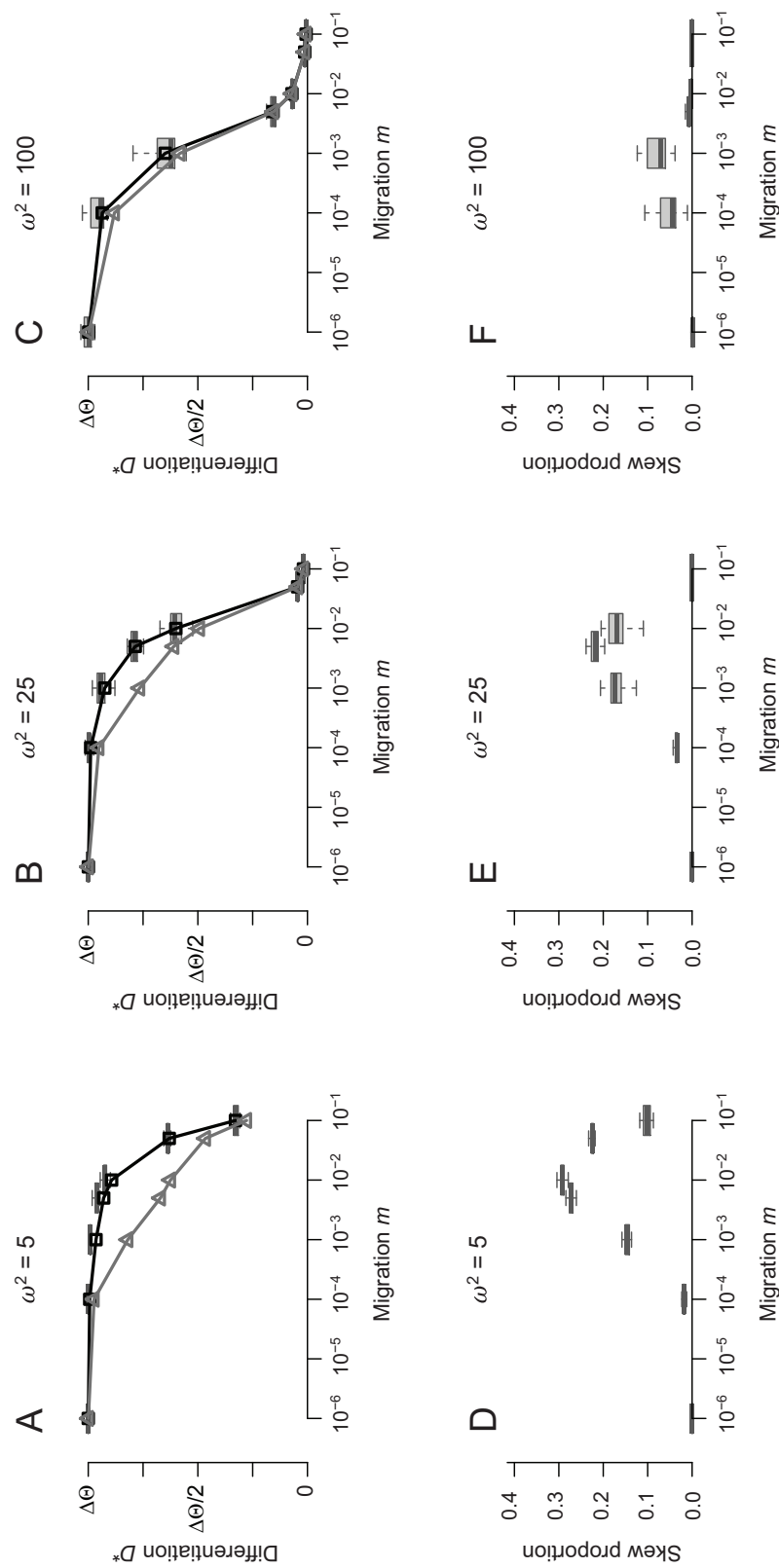
#### *With Evolvable Effects of Each Locus*

In a second set of simulations (fig. 4), we used the same assumptions as in Yeaman and Guillaume (2009), namely, that there was a continuum of possible allelic values at each locus. Each locus mutated with rate  $\mu = 10^{-4}$ , and mutations were drawn from a normal distribution with mean 0 and variance  $\alpha^2 = 0.01$ , with the value added onto any previous allelic value. Because the mean of the distribution of mutations is 0, mutation does not affect the local mean genotypic value.





**Figure 3:** Effect of individual loci in the simulations where allelic effects are fixed, for different values of  $a$ , the effect of the major locus. The major-effect locus is shown with open diamonds; another locus, of effect 0.1, is shown with open triangles (the bars represent the confidence intervals); the filled gray circles (on the second line) correspond to the whole trait. A–C, Frequency of the “+” allele at the two loci in the patch with  $\theta = -1$ . D–F, Contribution of individual loci (open symbols) to the third moment of the distribution of traits (filled circles).



**Figure 4:** Output of the simulations when allelic effects evolve, for different values of  $\omega^2$  ( $1/\omega^2$  is the strength of selection). A–C, Equilibrium phenotypic divergence between two patches in the simulations (box plots) and the corresponding expectations from equations 9 (black rectangles) and 10 (gray triangles; Gaussian approximation) as a function of the migration rate (evaluated with  $v^*$  and  $\zeta^*$ , the postselection variance and third moment, respectively). D–F, Proportion of the divergence due to the skew ( $\zeta^*/(\Delta\theta v^* + \zeta^*)$ ).

The results presented in figure 4 show that nonnegligible levels of skew evolve in the continuum-of-allele model, causing large discrepancies with the Gaussian model predictions (fig. 4A–4C). As it did above, taking account of the genetic skew greatly improves our predictions of the equilibrium divergence, using equation (9). The second row in figure 4D–4F shows that between 20% and 30% of the divergence at strong-to-intermediate stabilizing selection and intermediate migration rates is due to the asymmetry of the distribution, where discrepancies with Gaussian predictions are highest (the plots represent  $\zeta^*/(v^*\Delta\theta + \zeta^*)$ ).

These results indicate that the genetic architecture of the divergence likely incorporates evolved loci of major effects. The timescale of the simulations ( $10^6$  generations) allowed for this buildup of major-effect alleles from uniform genetic architectures at generation 0. This phenomenon has already been described in greater detail by Yeaman and Whitlock (2011), who showed that under divergent selection and at intermediate dispersal rates, one major locus eventually evolves and becomes responsible for most of the divergence between two populations. In accordance with the results of the diallelic simulation model (and with Yeaman and Guillaume 2009), this nonuniform genetic architecture then generates large amounts of skew in the distribution of genetic values and departures from Gaussian assumptions.

### Discussion

Without a priori assuming Gaussian distributions of genotypic values or phenotypic values, we derived an expression for the expected phenotypic divergence between two populations at migration-selection balance, using an assumption of weak selection. This expression is unclosed: it depends on the levels of variance and skew maintained in the population, which are themselves variables of the model and depend on population parameters, such as the strength of selection and the proportion of migrants at each generation, but also on the genetic architecture of the trait. Still, this derivation provides the analytical confirmation that neglecting the skewness of distributions can lead to underestimation of predictions of population differentiation when selection is spatially heterogeneous (Lopez et al. 2008; Yeaman and Guillaume 2009). Our analytical predictions match results from individual-based simulations, quantitatively improving previous predictions made with the assumption of Gaussian distributions (Hendry et al. 2001; Yeaman and Guillaume 2009).

As equation (9) is unclosed, the variance and skew have to be estimated from the simulations. This is because every moment of the distribution is itself a function of higher moments; further assumptions are required to be able to “cut” this chain of moments (as is done, for instance, in

island-continent models [Tufto 2010; Chevin and Lande 2011] but also in a two-patch model under the assumption of clonal reproduction [Débarre et al. 2013]). Our equation (9) hence requires information about the variance and skew of the distribution of genotypic values; more precisely, it requires their values before migration, while census time in the life cycle is after migration. Huisman and Tufto (2012) argued that the difference between the predictions of Yeaman and Guillaume (2009) and those of Hendry et al. (2001) may be due to this difference of timing of evaluation of the higher moments, more than to the skew itself. However, our simulations indicate that the timing of evaluation of these two moments has little influence on the predicted divergence (see fig. 1). Our simulations therefore confirm that the main difference between the predictions derived using equation (9) and the ones made assuming Gaussian distributions (eq. [10]) relies on the inclusion or exclusion of the skew term.

The amount of genetic skew is strongly affected by the genetic architecture of the trait under divergent selection and is greatest when divergence tends to be driven by one locus or tightly linked clusters of loci with alleles of large effect. This is, in particular, the case when allelic effect sizes can evolve (Yeaman and Whitlock 2011). When all loci have equal, small, and fixed effects, however, less skew tends to be generated. In this case, under a wide range of migration values, assuming Gaussian distributions remains a very good approximation.

From the results discussed here and in other recent studies, it is clear that the size and linkage relationships of alleles play an important role in determining the response to heterogeneous environments. Large-effect alleles are more resistant to swamping under high rates of gene flow (Lenormand 2002; Yeaman and Whitlock 2011; Geroldinger and Bürger 2014; Yeaman 2015) and are therefore more likely to contribute to local adaptation. From the quantitative-genetic perspective, once divergence has evolved, architectures with large-effect alleles tend to result in more genetic skew, leading to more efficient responses to selection than with a symmetric distribution with the same variance. Thus, traits with architectures characterized by large-effect alleles are also likely to be more highly diverged, relative to those with many small-effect alleles. To view these results from another perspective, finding evidence of substantial genetic skew in a locally adapted population (for instance, a third-moment-to-variance ratio of about 0.5 or higher, which, with the parameters of figs. 1 and 4, leads to a proportion of divergence due to the skew of 0.2 or higher) may suggest the presence of a large-effect locus, which could merit further genomic study.

From the population-genetics perspective, genes of major effects are expected to be involved in adaptation, as shown by Orr (1998), building on Fisher's (1930) geomet-

rical model. The empirical literature on quantitative trait locus studies seems to support this expectation (Lande 1983; Agrawal et al. 2001; Orr 2001; Slate 2005), although others have argued that most trait variation is due to small-effect alleles (Mackay et al. 2009; Rockman 2012). Joining population- and quantitative-genetics approaches, Lande (1983) showed that selection on genes of major effect must be strong in order to overcome their deleterious pleiotropic effects and substantially contribute to adaptive evolution. These negative pleiotropic fitness effects also play a prominent role in Fisher's geometrical model and lead to the expectation of a low frequency of large-effect mutations fixed during adaptation (Orr 1998). By contrast, our approach remains univariate: we do not account for deleterious side effects (in another trait dimension) of the segregating alleles. The question thus remains whether the evolution of loci of large effect may be impeded by pleiotropy in our case, which is likely. The effects of pleiotropy can be looked at similarly to Guillaume (2011), where the trait under divergent selection is pleiotropically linked to a trait under uniform stabilizing selection between populations. When the genetic correlation is large between the traits, the equilibrium divergence at migration-selection balance is smaller, and the trait under uniform selection also becomes differentiated (Guillaume 2011). This correlated divergence will thus cause additional selection on the pleiotropic mutations and may favor mutations with large effects on both traits. Interestingly, in situations with large correlated divergence, the genetic skew of the trait under divergent selection was substantial (see supplementary material in Guillaume 2011), suggesting the presence of pleiotropic mutations with large effects.

While quantitative genetics has proven incredibly useful for making practical predictions about evolution in natural environments and selective breeding, its fundamental assumption, that the underlying details of genetic architecture can be safely ignored, can cause us to overlook some interesting and important consequences of evolution. The underlying genetic architecture can shape the distribution of traits in ways that can be represented in quantitative-genetic models but are not themselves predictions that result from these models. Population-genetic models, on the other hand, explicitly predict that large-effect alleles should contribute to local adaptation. Here, we used simulations to show that large-effect alleles matter for the accuracy of quantitative-genetic models; another article in this issue (Yeaman 2015) shows how quantitative-genetic models can make more accurate predictions about adaptation than their population-genetic counterparts when there are many small-effect alleles that contribute to divergence. Taken together, these articles illustrate how population- and quantitative-genetic models complement each other and that the assumptions and constraints inherent to one ap-

proach can be relaxed, explored, and interpreted in light of the other.

### Acknowledgments

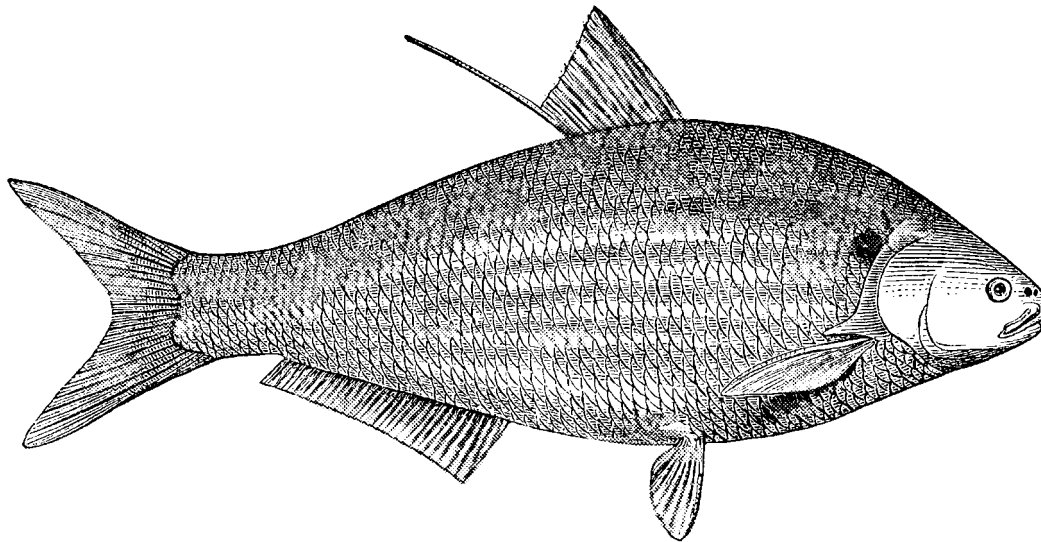
We thank M. Whitlock for giving us the chance to contribute to this special issue. We also thank R. Bürger, T. Day, J. Hadfield, J. Kelly, K. Lotterhos, S. Otto, M. Scott, T. Veen, M. Whitlock, Axios Review, and five anonymous reviewers for comments on the manuscript. F.D. acknowledges funding from University of British Columbia's Biodiversity Research Centre (Natural Sciences and Engineering Research Council Collaborative Research and Training Experience [CREATE] Program in Biodiversity Research) and from the Wissenschaftskolleg zu Berlin. S.Y. was supported by a Genome Canada/Genome British Columbia grant to the AdapTree project. F.G. was supported by the Swiss National Science Foundation (grants PZ00P3\_141987 and PP00P3\_144846). The simulations were run on Westgrid.

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Symposium Editor: Michael C. Whitlock



"If these *Dorosomæ* are left to themselves, unvisited by others later from the coast, will they in time become so far changed by the change in their surroundings as to be a different species? We thought them distinct in 1860, and the *Dorosoma*, from this same pond, is a different looking fish now, in 1870, from what it was then." From "Notes on Fresh-Water Fishes of New Jersey" by Charles C. Abbott (*The American Naturalist*, 1870, 4:99–117).